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EXAMINER

O DELL, DAVID K

ART UNIT

PAPER NUMBER

1609

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No. 10/525,303	Applicant(s) BERNSTEIN ET AL.	
	Examiner David K. O'Dell, Ph.D.	Art Unit 1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on February 23, 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-10 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

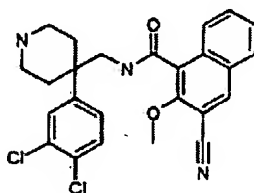
1. Claims 1-10 are pending in the current application.
2. The instant application is a 371 of PCT/SE2003/001329, filed August 26, 2003, which claims the priority of Application No. 0202567-4 filed in Sweden on August 29, 2002 and Application No. 0202986-6 filed in Sweden on October 9, 2002, is acknowledged.

Objections

3. The disclosure is objected to because of the following informalities: Applicant's chemical structure has divalent uncharged nitrogen, which is not known. The examiner has assumed that H is present, however such structural representations are inconsistent with accepted practices of structure drawing in organic chemistry (all non-carbon (hetero) bonded hydrogens must be shown in order to avoid ambiguity). A picture of an example of this structural representation is provided below taken from pg. 16 of the specification; this error is repeated throughout the specification. Appropriate correction is required.

Example 3: 4-(3,4-Dichlorophenyl)-4-(3-(3-cyano-2-methoxynaphth-1-yl)-3-oxo-2-azaprop-1-yl)piperidine.

The title compound of the following structure



Claim Rejections 35 U.S.C 112/101

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 9 provides for the use of the compounds of, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. Claim 9 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd. App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds of structural diagram I (claim 1), it does not reasonably provide enablement for the multivariate structures contained in the claim where R^1 - R^2 are varied substituents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to prepare the compounds of the invention commensurate in scope with these claims. As per MPEP:

A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court in *In re Ghiron*, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. **The same can be said if certain chemicals are required to make a compound or practice a chemical process.** In *re Howarth*, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981). (emphasis added)

Based on applicants disclosure (on pages 16 and 17 of the specification, reproduced below for clarity),

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The requisite 1-N-BOC-4-(3,4-dichlorophenyl)-4-(3-(3-cyano-2-methoxynaphth-1-yl)-3-oxo-2-azaprop-1-yl)piperidine was prepared as follows:

- 25 a) 1-N-BOC-4-(3,4-dichlorophenyl)-4-(3-(3-cyano-2-methoxynaphth-1-yl)-3-oxo-2-azaprop-1-yl) piperidine.

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To a stirred solution containing 1-N-BOC-4-aminomethyl-4-(3,4-dichlorophenyl)piperidine (260.8 mg, 0.726 mmol), 3-cyano-2-methoxy-1-naphthoic acid (164.6 mg, 0.724 mmol), HOBT hydrate (290 mg, 1.89 mmol), N-methylmorpholine (0.17 mL), and DCM (15 mL) was added 1-(3-(dimethylamino)propyl-3-ethylcarbodiimide hydrochloride (215.5 mg, 1.12 mmol). After 72h, the mixture was diluted with 30% hexane/EtOAc, washed successively with water (2X), 0.1 N aq. HCl (2X), sat. aq. NaHCO₃, dried, filtered, and concentrated. The residue was purified by chromatography (0-1% MeOH/DCM) to give the title compound as a white, foamy solid. MS m/z 468.

b) 1-N-BOC-4-aminomethyl-4-(3,4-dichlorophenyl)piperidine

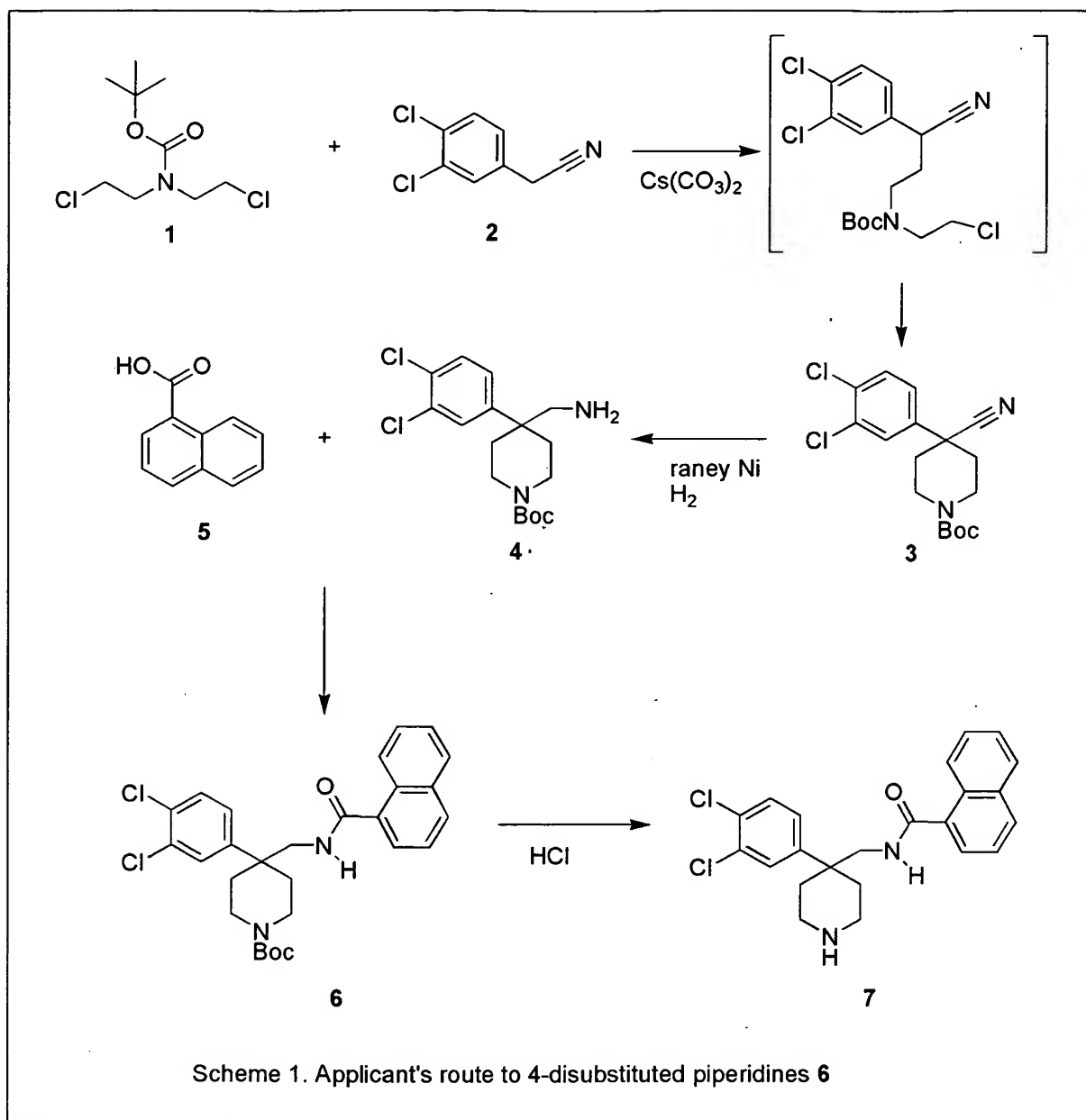
- 0 A mixture containing 1-N-BOC-4-(3,4-dichlorophenyl)-4-cyanopiperidine (5.25 g, 14.78 mmol), Raney Ni catalyst (5g of 50% aq. slurry), EtOH (175 mL), and ammonium hydroxide (88 mL) was placed under a hydrogen atmosphere (50 psi) and agitated (Parr apparatus) for 18 h. The mixture was filtered through diatomaceous earth, concentrated, and purified by chromatography (0-5% MeOH/DCM) to give the title compound as an off-white solid. MS m/z 344 (M+1-CH₃).
5 ¹H NMR (CDCl₃) δ 7.44 (d, 1H), 7.38 (d, 1H), 7.15 (m, 1H), 3.7 (br d, 2H), 3.07 (m, 2H), 2.76 (s, 2H), 2.08 (br d, 2H), 1.71 (m, 2H), 1.44 (s, 9H).

c) 1-N-BOC-4-(3,4-dichlorophenyl)-4-cyanopiperidine

- A solution containing bis(2-chloroethyl)-N-BOC amine (described in US Patent 5,661,163) (8.15 g, 33.67 mmol), 3,4-dichlorophenylacetonitrile (5.05 g, 27.17 mmol), and DMSO (50 mL) was stirred at RT and solid cesium carbonate (17.6 g, 54.02 mmol) was added (in portions) over 10 minutes. After 20 h, additional cesium carbonate (1.7 g) was added, and the mixture stirred for an additional 72 h. The mixture was partitioned between water and EtOAc, the aq. layer was removed, and the organic layer washed successively with additional water, 0.1M aq. HCl (2X), sat. aq. NaHCO₃, and brine. The organic layer was dried, filtered, concentrated, and the residue triturated (3:1 hexane/ethyl acetate) to give the title compound as an off-white solid, m.p. 142-145 °C. MS m/z 255. ¹H NMR (CDCl₃) δ 7.55 (d, 1H), 7.49 (d, 1H), 7.32 (m, 1H), 4.3 (br d, 2H), 3.18 (br t, 2H), 2.07 (d, 2H), 1.89 (m, 2H), 1.48 (s, 9H).
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Scheme 1 was constructed and is presented here for discussion of the synthetic route to these compounds and the limitations therein.



Compounds bearing a vast list of possibilities for R¹, R², R³, R⁴ have been claimed in claims 1-3 and very little guidance has been provided on how to do so. A detailed discussion of each limitation of the synthesis as it relates to the claims at hand

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(claims 1-3) will be provided. The applicant needs substituted benzyl nitriles of the type **2** (Scheme 1) and no guidance has been given as to how one might arrive at these compounds. These are very specialized compounds and *we are not given a route to a single one?* Most of them are not commercial compounds. We are not told how to make them, thus the public cannot be in possession of the invention if they cannot make it. If the vast array of compounds **2** were available many will not participate in the synthesis given (Scheme 1), thus the scope of the claimed substituents R_4 is not enabled. In particular where **2** and thus R_4 is a nucleophile such as " NR^aR^b , $CH_2NR^aR^b$, SR^a , CH_2OR^a , OR^a , $C(O)R^c$," will attack the dichloride **1**, preferentially leading to other products. The use of Raney Ni/ H_2 necessarily precludes many substituents listed as R_4 in claims 1-3. The following groups for R_4 are not enabled due to the use of Raney Ni/ H_2 :

A) " $(CH_2)_jG(CH_2)_k$ or $G(CH_2)_jG$, where G is oxygen or sulfur, j is 1, 2, 3 or 4, and k is 0, 1 or 2; m is 1, 2 or 3 where at least one R moiety is other than hydrogen...."; " R^a and R^b together are $(CH_2)_jG(CH_2)_k$ or $G(CH_2)_jG$, and n is 0, 1, 2 or 3..." and " SR^a ". Groups that contain sulfur will undergo desulfurization, as is well known in the art (Hauptman and Walter, *Chem. Rev.* **1962**, 62, 347.)

B) Surprisingly nitrile (CN) is listed as a possible permutation of Formula I's R_4 , yet we know from the disclosure that this nitrile will be reduced to the amine with Raney Ni/ H_2 (**3** to **4**, Scheme 1). Thus it is not enabled.

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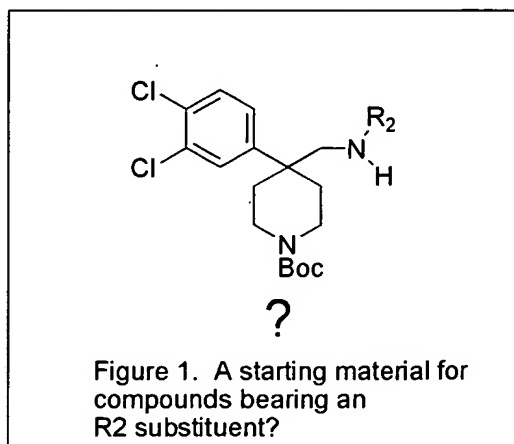
C) Olefins and alkynes, where R_4 is C_{2-4} alkenyl, C_{2-4} alkynyl, will be reduced as is well known in the art (Fieser and Fieser, *Reagents for Organic Synthesis*, Vol. 1 Wiley: NY, 1974, pg. 723-730).

D) Ketones and aldehydes where R_4 is $C(O)R_c$, or CO_2R_c can also be reduced as is known in the art (Mitchell and Lai *Tetrahedron Letters* **1980**, 21, 2637).

E) Where R_4 halogen and in the ortho (2-position relative to the benzyl nitrile) of the phenyl ring, upon reduction of the nitrile an intramolecular cyclization will occur to give spirocyclic indolo-piperidines as taught by Ong et. al. *J. Med. Chem.* **1983**, 26, 981-986.

It is also known that Raney/Ni will dehalogenate aryl halides, resulting in what is formally a replacement of halogen with hydrogen (Fieser and Fieser, *Reagents for Organic Synthesis*, Vol. 1 Wiley: NY, 1974, pg. 726), although applicant seems to have provided conditions that prevent this reaction.

F) Applicant also makes claims to compounds where R_2 is other than H (claims 1-4 and dependent) and no guidance is provided as to how we can arrive at these compounds. It would seem that a starting material as shown in Figure 1, is required, yet we do not have any guidance as to how one may obtain such compounds.



G) In addition the naphthoic acids such as **5** (Scheme 1) required for the scope of this invention are not commercial. Thus the substituent R₁ depends upon these compounds. It is recognized that applicant makes reference to a prior commonly assigned application WO 00/20389 for the preparation of a good portion of these and these will be considered allowable, particularly where applicant has working examples in synthetic schemes, but no others.

As per MPEP:

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

- (A) *The breadth of the claims;*
- (B) *The nature of the invention;*
- (C) *The state of the prior art;*
- (D) *The level of one of ordinary skill;*
- (E) *The level of predictability in the art;*
- (F) *The amount of direction provided by the inventor;*
- (G) *The existence of working examples; and*
- (H) *The quantity of experimentation needed to make or use the invention*

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

As applied to the claims at hand (claims 1-3):

A) The claims are very broad. B) This is a chemical invention, thus we need to be able to make the compounds in order to use them. C) The state of the art shows that many reactions can occur with compounds **2**. D) The level of ordinary skill is one with a basic knowledge of organic chemistry. E) Chemistry is inherently unpredictable (*In re Marzocchi*, 169 USPQ 367, *In re Fischer*, 166 USPQ 18). F) The inventor gives us little or no guidance (especially on the origin of compound **2**). G) The applicant has no

working examples of the substituents listed above. H) An undue amount of experimentation would be needed to make these compounds.

6. Claims 8-10 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. Disclosure of the activity of the compounds and dosages that are critical or essential to the practice of the invention, but not included in the claims is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The only information given as to what these compounds may do, at least in the pharmacological sense, is on pg. 12 of the disclosure "Individual IC_{50} values were reported, along with pIC_{50} . When the two IC_{50} 's obtained for a compound differed by more than 3-fold that compound was assayed one or two more times to redetermine the value. Compounds of the present invention exhibit a K_i in the range of 1 to 100 nM in the SERT assay and have an IC_{50} 's in the range 1 to 100 nM in FLIPR assay." The applicant has given ranges of two orders of magnitude for each individual assay, without reference to a known compound that is an agonist/inhibitor and the variability in these assays make evaluation of therapeutic value difficult. For example in the case of the NK-1 receptor in transfected cells, overexpression of a GPCR can lead to many false positives in a FLIPR assay, due to high constitutive activity and the low threshold of activation. The situation is further compounded by the fact that it is possible for a single compound to be very different things at each target. In the instant case we do not know whether the compounds are partial agonists at the NK-

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1 receptor. It is possibly that some compounds are both SERT inhibitors and partially active at the NK-1 receptor and vice versa, or both potent inhibitors of SERT and potent antagonists at the NK-1 receptor. Applicant seems to believe these compounds are the later although no support has been provided for this assertion. Moreover, even if this dual activity was possessed by the compounds of the invention, one cannot predict *a priori* what the outcome of such complex pharmacological behavior would be in the complex diseases of claim 10. The article cited by the authors (Ryckmans, T., et al., Bioorg. Med. Chem.Lett. (2002), 12, 261). suggests that these kinds of compounds might be useful for treatment of depression and they may well be but no such evidence is provided in the instant case. The "how to use" requirement of 35 U.S.C. 112 are not met by disclosing a pharmacological activity of the claimed compounds if one skilled in the art would not be able to use the compounds effectively without undue experimentation (In re Diedrich (CCPA 1963) 318 F2d 946, 138 USPQ 128; In re Gardner et. al. (CCPA 1970) 427 F2d 786, 166 USPQ 138). In regard to claim 10, depression is the only disease where such treatment *might* be efficacious, however this is debatable as stated in a recent review (Rosenzweig-Lipson et. al. *Pharmacology & Therapeutics* **2007**, 113, 134-153) pg. 140 paragraph 3 sentence 2:

"Although the NK-1 antagonist
aprepitant was not proven efficacious in Phase III depression
trials (Keller et al., 2006), it is conceivable that the combination
of aprepitant with an SSRI might result in rapid onset of
antidepressant effects. To this end, NK-1 antagonists have been

shown to potentiate the neurochemical effects of SSRIs in preclinical studies (Guiard et al., 2004). Whether this combination or other non-monoaminergic mechanisms will produce rapid onset antidepressant effects remains to be answered.”

Thus the state of the art in the area of these dual antagonists is murky at best. Even if there was a correlation of the pharmacological activity with a clinical manifestation, we have only *in-vitro* testing of these compounds and no *in-vivo* data. Without at least animal studies of *in-vivo* activity one cannot believe that these compounds will behave as therapeutics in those suffering from depression. Moreover, even if these compounds were evaluated simply as NK-1 antagonists, a recent review article (McLean, S. *Current Pharmaceutical Design* **2005**, 11, 1529, pg. 1542 paragraph 3) states, that:

In summary, clinical studies with three different compounds demonstrate antidepressant efficacy in both mildly depressed as well as melancholic patients. Furthermore, the favorable side effect profile of the agents suggests a viable therapy particularly for people experiencing significant sexual side effects with currently available antidepressants. This has to be balanced against a number of trials in which NK1 receptor antagonists failed to show activity. In addition to the previously mentioned negative trials, NKP608 another NK1 receptor antagonist was reported on the Novartis web site to have been terminated from further development for depression although it is unclear whether this was due to side effects or lack of efficacy. To date there are three positive trials in depression, one positive trial in panic, several failed trials and at least 2 negative studies.

It seems very unlikely that one skilled in the art would know what to do with these compounds. The other exhaustive list of diseases in claim 10 have no credibility for

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treatment given the mechanism that applicant alleges and the current knowledge in the art. The factors outlined in *In re Wands* mentioned above apply here, and in particular

As per the MPEP 2164.01 (a):

"A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to use"...."the claimed invention without undue experimentation. *In re Wright* 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has no working examples in this unpredictable art without undue experimentation.

8. Claims 1, 7, 8, & 9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. To satisfy the written description requirement applicant must convey with reasonable clarity to one skilled in the art, as of the filing date that applicant was in possession of the claimed invention. Applicant's claims are drawn to "in vivo hydrolysable precursor"s. The specification gives no guidance as to what these compounds are. Thus all claims reciting "in vivo hydrolysable precursor" are rejected. Applicant is attempting to claim a compound by what it does rather than what it actually is. This does not let us know what the invention actually is. It is not possible to predict *a priori* what an "in-vivo hydrolysable precursor" is. This recitation of functional language without any correlation to physicality does not meet the written

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description requirement. Claims employing functional language at the point of novelty, such as applicant's, neither provide those elements required to practice the inventions, nor "inform the public" during the life of the patent of the limits of the monopoly granted. These expressions could encompass a myriad of compounds and applicants claimed expression only represents an invitation to experiment regarding possible compounds.

Allowable Subject Matter

9. Claim 4 has been rejected for written description, and scope of enablement, but could be allowable if rewritten in independent form without the words "in-vivo hydrolysable precursors", and if applicant shows that all the substituents of Ar are attainable as set forth in the above enablement rejection. Although they are remarkable similar to the compounds of the invention of Bao et. al PCT/US99/25066 and U.S. Patent 6,303,637, (Bao claims naphthyl, but fails to make them, the only difference between compounds of the '637 patent and the instant case, however the utility is different). It is not clear why one would use naphthyl instead of phenyl to achieve the dual NK-1 and SERT activity. The courts have evidently decided that naphthyl is not obvious over phenyl *Ex parte Kaiser and Zirkle*, 146 USPQ 548 (Bd. Pat. App. & Int. 1964), *In re Jones*, 65 USPQ 480 (C.C.P..A. 1945).

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell, whose telephone number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisors, Cecilia Tsang can be reached at (571)-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.


CECILIA TSANG
SUPERVISORY PATENT EXAMINER